REMARKS

Status of the Claims

Claims 2, 3, 6, 9-19, 21-34, 37-47 and 49-84 are pending in the application.

Claims 21-27 and 49-83 have been withdrawn from consideration by the Office on the basis that they are drawn to non-elected subject matter.

Claims 2, 3, 6, 9-19, 28-34, 37-47 and 84 remain under consideration with entry of this Submission.

Summary

Claims 2, 3, 6, 9-19, 28-34, 37-47 and 84 are pending in the application and were examined in the Office Action dated 17 August 2009. Applicants note with appreciation that the following rejections have been withdrawn by the Office: **(i)** the rejection of claim 6 under 35 U.S.C. §112, second paragraph; and **(ii)** the rejection of claim 6 under 35 U.S.C. §112, second paragraph. However, the Office has maintained the rejection of claims 2, 3, 6, 9-19, 28-34, 37-47 and 84 under 35 U.S.C. §103(a) as unpatentable over U.S. Patent No. 6,331,311 to Brodbeck et al. ("Brodbeck '311") in view of U.S. Patent No. 6,130,200 to Brodbeck et al. ("Brodbeck '200") and Penco et al (1998) *Polymer International* 46:203-216 ("Penco") and Ravivarapu et al. (2000) *European Journal of Pharmaceutics and Biopharmaceuticals* 50:263-270 ("Ravivarapu"). Applicants respectfully traverse the remaining claim rejection for the following reasons.

The Rejection under 35 U.S.C. §103

Claims 2, 3, 6, 9-19, 28-34, 37-47 and 84 stand rejected under 35 U.S.C. §103(a) as unpatentable over Brodbeck '311 in view of Brodbeck '200, Penco and Ravivarapu. In particular, the Office asserts that one possible interpretation of the Markush language used in Brodbeck '311 is that they "teach mixtures of lactic acid based polymers of a wide molecular weight range [and] this would include low, medium and high molecular weight polymers." Office Action at page 4. The Office then looks to the secondary reference to Ravivarapu , where the degradation rates of two distinct, individual solid

microsphere compositions were compared, and then asserts that "[t]hese studies illustrated the concept of blending polymers or microspheres of varied characteristics in achieving modified drug release. It is then understood ... that low MW PLGA degrades faster and results in faster drug release while higher MW PLGA degrades more slowly thus manifesting a slower drug release and mixtures of the different MW polymers produce a blended release profile." Office Action at page 7. The remaining secondary references are used by the Office to show that various single components of applicants' recited composition are not new. Office Action at page 5. The Office then concludes that it would have been *prima facie* obvious to have combined the cited references in such a way as to arrive at applicants' claimed invention. Office Action at pages 7-9. Applicants respectfully traverse the rejection for the following reasons.

Applicants respectfully submit that the Office's assertions are fundamentally flawed, both technically and factually. In light of this flaw, the only possible manner in which to arrive at applicants' claimed compositions from the combination of prior art is an impermissible hindsight reconstruction of those compositions, using applicants' own specification as a template with which to piece the various parts together. The ordinarily skilled person would simply not make the same conclusions that the Office has asserted.

In particular, the Office asserts that the skilled person would interpret the Markush language used in Brodbeck '311 to "teach mixtures of lactic acid based polymers of a wide molecular weight range" and that "this would include low, medium and high molecular weight polymers." Office Action at page 4. This assertion is factually incorrect since Brodbeck '311 clearly does not teach such a combination. Brodbeck simply provides a wide variety of polymer families that a single polymer system can be selected from, wherein the selected polymer could have a molecular weight over a wide range of possibilities. Brodbeck '311 represents a single publication from a huge number of publications about injectable depot systems, dating back into the 1980's, wherein single polymer species have been used to provide depot systems. This assertion is also technically incorrect since the ordinarily skilled person would understand that homogeneity is a critical feature of a pharmaceutical depot composition. The skilled person would understand that if one were to produce a depot that could have varied

release characteristics depending upon how well one combined various elements (such as different polymers having different molecular weights), such a product may not have a chance of gaining regulatory approval. One of the most critical and essential showings that a pharmaceutical manufacturer must make to gain marketing authorization is that it has a product that will behave exactly as labeled, from lot to lot, and from production site to production site. Mixing up polymers species into a single composition adds a huge deal of variability to a manufacturing process for an injectable depot composition. If the polymers are not blended in exactly the same way, to provide a homogenous polymer matrix every single time, there is a very good chance that individual depot dosage forms will have different delivery rates/characteristics, where a depot with a portion containing too much of one molecular weight polymer will behave differently from a different depot with a portion having too much of the other polymer species. Accordingly, making the intellectual jump from Brodbeck '311's actual teachings and applicants' systems would entail having to change the standard practice in the injectable depot business of using a single polymer species AND would further entail forcing someone having ordinary skill in the pharmaceutical arts to make a design choice that would have been expected to produce a drug product that could not expect to gain regulatory approval.

The Office further asserts that the ordinarily skilled person would look to the Ravivarapu reference (where the degradation rates of two distinct, individual solid microsphere compositions were compared) and somehow extrapolate that a single gel composition could be formed from a mixture of polymer species having different molecular weights. As noted above, the Office specifically asserts that the Ravivarapu studies "illustrated the concept of blending polymers or microspheres of varied characteristics in achieving modified drug release. It is then understood ... that low MW PLGA degrades faster and results in faster drug release while higher MW PLGA degrades more slowly thus manifesting a slower drug release and mixtures of the different MW polymers produce a blended release profile." Office Action at page 7. Here again, applicants respectfully submit that this is both factually and technically incorrect.

As applicants set forth in their previous Response (dated 17 April 2009), solid microparticle compositions and liquid gel compositions behave in entirely different ways to provide for controlled release systems. Solid microparticle compositions rely upon the hydration, swelling and subsequent breaking apart of the solid particles (over time) to provide for controlled release of the drug agent that is encased in the solid polymer system. Break up of the solid matrix exposes the drug to the aqueous tissue for release. The left-over, broken polymer fragments from the microspheres then bioerode over time. Liquid gel compositions do not break apart. Liquid gel compositions remain intact in the area of administration, and controlled release of the drug agent occurs by diffusion of the drug through the liquid/gel matrix. After all of the drug has diffused out of the polymer depot, the left-over matrix bioerodes over time. In the Response dated 17 April 2009, applicants pointed out this fundamental difference between the two systems, and further pointed out that the ordinarily skilled person understands this fundamental difference between the two systems and does not expect attributes of a solid polymer system to remain identical when one moves to liquid/gel polymer systems. The Office has not responded to this traversal in the instant Office Action. Accordingly, the Office's assertion that the skilled person would have understood Ravivarapu to teach blending of polymers into a single liquid/gel composition on the basis of behavior of their solid microparticle compositions is technically incorrect. The ordinarily skilled person would simply not make that assumption, knowing of the fundamental differences between solid and liquid/gel systems.

The Office's assertion is also factually incorrect. Ravivarapu teach production of single, discrete microsphere compositions. They produce these compositions using single polymer species, and thus provide a collection of discrete compositions having discrete release performance. Those compositions may be combined and co-administered as the Office has suggested, but what the Office has failed to recognize is that polymers were not blended to produce a single composition. The reason for this has already been discussed herein above. Homogeneity and reproducibility are key considerations for someone ordinarily skilled in the pharmaceutical arts. That skilled person knows and understands that he/she can produce discrete microsphere compositions, using a single

polymer species for each composition, and that those populations of microspheres will be the same from lot to lot, and from manufacturing site to manufacturing site. That same skilled person then knows and understands that specific amounts (by weight or by volume) of each individual composition can be combined into a single administration, and that each of those specific combinations of compositions will have the same drug delivery rate performance. The Office has confused this understanding with applicants' recited compositions, where it is required that different polymer species be combined to produce a single composition (and not that several discrete compositions can be combined and then co-administered).

Accordingly, the premise that the Brodbeck '311 liquid/gel systems would be easily modified using inspiration from the solid microspheres of Ravivarapu is incorrect. The ordinarily skilled person would simply not look to rapidly degrading solid microsphere systems in order to improve or modify the Brodbeck '311 liquid/gel. In like manner, the ordinarily skilled person would not look to liquid/gel-based technologies to improve or modify solid microsphere systems. The two systems are simply incompatible and operate by entirely different mechanisms of action. Modifying a liquid/gel to hydrate and degrade more rapidly would disrupt that system and frustrate the basic mechanism of action (controlled diffusion of the active agent through the intact gel matrix). Modifying a solid microparticle to resist hydration and degradation would frustrate the basic mechanism of action of that system (rapid hydration and degradation of the solid matrix to expose and release the active agent).

This is strong evidence of nonobviousness as noted by the Supreme Court in *KSR* emphasizing that consideration of prior art that teaches away from the claimed invention is also relevant to the determination of obviousness. In particular, the Court stated that ***"when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious."*** *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). See also, *Dystar Textilfarben GmbH v. C.H. Patrick Co.*, where the Federal Circuit stated that "[once] all claim limitations are found in a number of prior art references, the factfinder must determine '[w]hat the prior art teaches, ***whether it teaches away from the claimed invention***, and whether it motivates a

combination of teachings from different references.' *Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 80 U.S.P.Q.2d 1641, 1646 (Fed. Cir. 2006), *citing In re Fulton*, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004) (*emphasis added*). Finally, as stated in the MPEP, "[i]f [the] proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. M.P.E.P § 2143.01. The Federal Circuit has stated a similar principle in *In re Gordon*, indicating that where the proposed modification would render the prior art invention unsatisfactory for its intended purpose, the prior art invention effectively teaches away from the proposed modification. *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984).

Accordingly, the Office's proposed combination fails to establish a *prima facie* showing of obviousness of applicants' recited compositions. A proper reading of Brodbeck '311 reveals that the Office's assertion of disclosure of mixtures of lactide polymers having different molecular weights is simply incorrect. The Office's reliance on the primary reference to Brodbeck '311 to teach applicants' recited mixtures of two or three different molecular weight lactide polymers is factually and technically incorrect. In addition, the ordinarily skilled person would not take guidance or inspiration from Ravivarapu's teaching of how to speed up hydration and degradation of solid microspheres and apply it to the Brodbeck '311 gel systems as argued by the Office. This would be expected to render the Brodbeck '311 gel unsatisfactory for its intended purpose. In light of this expectation, there cannot have been a reasonable expectation of success for the Office's asserted combination. The other secondary references to Brodbeck '200 and Penco add nothing to this fatal flaw in the Office's required *prima facie* showing of obviousness.

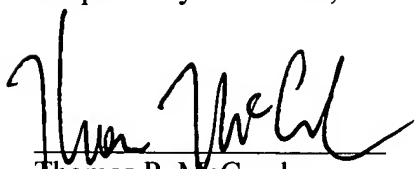
For all of the foregoing reasons, then, the rejection of claims 2, 3, 6, 9-19, 28-34, 37-47 and 84 under 35 U.S.C. §103(a) is improper. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

CONCLUSION

Applicants submit that the pending claims define an invention that is both novel and nonobvious over the cited art, and thus all claims are in condition for allowance. Acknowledgement of this by the Office in the form of an early allowance is thus respectfully requested. In addition, if the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, applicants invite the Examiner to contact the undersigned at (408) 777-4915.

The appropriate fee is either attached or authorized. If the Commissioner determines that an additional fee is necessary, the Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. **50-1953.**

Respectfully submitted,



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